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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,053	04/06/2000	James W. Williams	29666/35415	1413

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EXAMINER	
WANG, SHENGJUN	
ART UNIT	**PAPER NUMBER**
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/529,053	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Shengjun Wang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-42,45 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-42,45 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on May 2, 2007 has been entered.

2. It is noted that there are two claim 45. According 37 C.F.R. 1.126, the last claim is renumbered as claim 46

Claim Rejections 35 U.S.C. 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 46 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The newly introduced limitation "a pyrimidine compound without antiviral activity" lacks support from the application as originally filed. See, page 20 of the application. "A pyrimidine compound without antiviral activity" is a new concept for the application and constitutes a new matter.

Claim Rejections 35 U.S.C. 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 34, 35, 40, 41 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weithmann et al. (US Patent 5,556,870) in view of Hammer (AIDS 1996, vol. 10, suppl 3, s1-s11) and Colacino. .

7. Weithmann et al. teach a method of treating disorder in which interleukin 1 beta is involved. The disorders include viral infections, such as HIV or hepatitis, comprising administering leflunomide to the patient. See, particularly, the abstract and the claim. The dosage may range from 3-50 mg daily, but may be higher if required. See, particularly, column 3, lines 7-16.

Weithmann et al. do not teach expressly the employment of addition pyrimidine antiviral agent in the method.

8. However, Hammer teaches that several pyrimidine compounds, including uridine compounds, are known antiviral agents. See, particularly, page s3. Colacino teaches that uridine compound FIAU is also known to be useful for treatment of hepatitis and herpes infection. See, particularly, pages 125-126.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ a combination of leflunomide

compounds with other antiviral agents such as those known pyrimidine compounds Also, it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for same purpose in order to form third composition that is to be used for very the same purpose; idea of combining them flows logically from their having been individually taught in prior art; thus , the claimed invention which employ a combination of two known anti-viral agents sets forth prima facie obvious subject matter. See In re Kerkhoven, 205 USPQ 1069. Further, combination therapies for viral infection are known to be better than single agent therapy. See, Hammer, page s2, the paragraph of combination therapy.

9. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weithmann et al. (US Patent 5,556,870) in view of Hammer (AIDS 1996, vol. 10, suppl 3, s1-s11) and Colacino, and in further view of Flamand et al.

Weithmann et al., Hammer, and Colacino as whole do not teach expressly the employment of leflunomide for treatment of herpes infection.

However, Flamand et al. teaches that herpes infection is involved with interleukin 1 beta. See, particularly, the abstract.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ the method of Weithmann for treating herpes infections.

A person of ordinary skill in the art would have been motivated to employ the method of Weithmann for treating herpes infections, because herpes infection is known to be involved interleukin 1 beta. Further, the optimization of a result effective parameter, e.g., effective amount for a therapeutical dosage of a known therapeutical agent, is considered within the skill

of the artisan. See, In re Boesch and Slaney (CCPA) 204 USPQ 215. It is noted the effective amounts disclosed by Weithmann et al. are well within the effective amounts herein (from 0.1 mg/day to 80 mg/day, see pages 13-19).

10. Claim 34-42 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coghlan et al. (WO 94/24095), in view of McChesney et al. (Transplantation, Vol. 57, no. 12, page 1717-1722), and further in view of Hammer (AIDS 1996, vol. 10, suppl 3, s1-s11), and Colacino.

Coghlan et al. teaches compounds with general structures that encompass leflunomide or its active metabolite, and meet the limitation of general formula as defined in claims 38 and 44, the compounds have similar biological activity of leflunomide or its metabolite. See, particularly, the abstract, page 2, the examples and the claims. The expressly taught compounds includes those meet the leflunomide products (page 18-19 in the specification). Homologue of leflunomide (e.g., 5-methyl-isoxazole-4-carboxylic acid 2,2,2,trifloroethylamide) have been expressly disclosed (page 10, line 35). These compounds are known to be useful for treating or preventing infectious disease caused by pathogenic microorganism, such as hepatitis and cytomegalovirus infection, particularly, HCMV. See, page 3, lines 7-30, page 4, lines 23-32. Note, amide of malononitrile recited in claims 37 and 43 are keto tautomer of the leflunomide metabolisms as defined in claims 38 and 44, such as A771726, and would have been expected to be the same as those enol tautomers.

Coghlan et al. does not teach expressly the employment leflunomide or its metabolite, or the particular amount herein for treating viral infections. Coghlan et al. (WO 94/24095) do not teach expressly the employment of pyrimidine compound in the method.

11. However, McChesney et al. teaches that both leflunomide and A771726 are known to be effective in preventing viral infection. See, particularly, the abstract at page 1717, and the materials and method at page 1717-1718. Hammer teaches that several pyrimidin compounds, including uridine compounds, are known antiviral agents. See, particularly, page s3. Colacino teaches that uridine compound FIAU is also known to be useful for treatment of hepatitis and herpes infection. See, particularly, pages 125-126.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ the compounds taught by Coghlan et al., including both leflunomide and A771726, for treating or prevention viral infections such as hepatitis and CMV, and the others defined herein.

A person of ordinary skill in the art would have been motivated to employ the compounds taught by Coghlan et al., including both leflunomide and A771726, for treating or prevention viral infections such as hepatitis, CMV or other viral infections herein defined, because these compounds are known to be useful for treating or preventing infectious caused by pathogenic microorganisms, and viral infection in particular. Further, both leflunomide and A771726 are known to be similarly useful as the other compounds. Furthermore, the reference teaches certain compounds that are structural homologs of the instantly claimed leflunomide, i.e., they differ only by a CH_2 group. The instant compounds are structural homologs of the reference compounds when they differ only by a CH_2 group. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compound because such structurally homologous compounds are expected to possess similar properties. It has been held that

compounds that are structurally homologous to prior art compounds are prima facie obvious, absent a showing of unexpected results. In re Hass, 60 USPQ 544 (CCPA 1944); In re Henze, 85 USPQ 261 (CCPA 1950).

Further, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ a combination of leflunomide compounds, including those disclosed by Coghlan et al, with other antiviral agents such as those known pyrimidine compounds. Also, it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for same purpose in order to form third composition that is to be used for very the same purpose; idea of combining them flows logically from their having been individually taught in prior art; thus , the claimed invention which employ a combination of two known anti-viral agents sets forth prima facie obvious subject matter. See In re Kerkhoven, 205 USPQ 1069. Further, combination therapies for viral infection are known to be better than single agent therapy. See, Hammer, page s2, the paragraph of combination therapy.

Response to the Arguments

12. Applicants' remarks and the 132 declaration submitted December 21, 2007 have been fully considered, but are not persuasive.

13. The declaration of Dr. Water Atwood assert that the pyrimidine compounds recited in the application would be understood by ordinary artisan as without antiviral activity. However, it is noted the application does not particularly exclude antiviral pyrimidine compounds. The arguments as to the scope of "pyrimidine compounds" are not persuasive. Particularly, "pyrimidine compounds" defined by the application as those compounds having pyrimidine

moiety and are " useful either directly or as intermediates in pathways for supplying pyrimidine nucleotides (uridine, cytidine and thymidine). The antiviral agents cited on the record are deemed to meet such limitation. The examiner agrees that the application does not particularly *require* the "pyrimidine" be antiviral compound. But the application does not exclude any pyrimidine compounds with antiviral activity.

14. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the teaching, suggestion and motivation are found in the cited prior art and in the knowledge generally available to one of ordinary skill in the art. Particularly, both compounds herein are known to be useful as antiviral agents, the employment of the combination of the two compounds sets forth prima facie obvious subject matter.

15. In response to applicant's argument that the cited references do not discloses “enhance serum levels of uridine, cytidine or thymidine,” the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

16. Regarding the establishment of unexpected results, a few notable principles are well settled. It is applicant’s burden to explain any proffered data and establish how any results

therein should be taken to be unexpected and significant. See MPEP 716.02 (b). *The claims must be commensurate in the scope with any evidence of unexpected results*. See MPEP 716.02 (d). The claims read on any pyrimidine compounds, while the application merely shows the benefit of uridine (example 2), not all of its derivatives as herein claimed. Therefore, the claims are not commensurate in the scope with the evidence on the record.

17. Subject matters as claimed to claim 34, and limited to those wherein *pyrimidine compound* is uridine, orotic acid and orotidine would be favorably considered. Note, claim 42 read on uridine *compounds, i.e.* any derivatives of uridine.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shengjun Wang whose telephone number is (571) 272-0632. The examiner can normally be reached on Monday to Friday from 7:00 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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